Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 47-51, 53, 56-66, 68-69, 74-78, 80, 82, 84-89, 91, 94-104, 106-107, 112-116, 118-121, 123-128, 130, 133-143, 145-146, 151-155, 157-159 and 164-215 are pending in the application, with 84, 123, 167, 185, and 196 being the independent claims. Claim 215 has been added. Support for the newly added claim can be found, *inter alia*, at paragraph [0183] of the specification as filed. These changes are believed to introduce no new matter and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and further request that they be withdrawn.

Objection to the Specification

In the Office Action dated April 6, 2005 ("the Office Action") at page 4, the Examiner withdrew the objection to the Specification.

Claim Objections

In the Office Action at page 4, the Examiner withdrew the objection to claims 83 and 163.

Sequence Compliance

In the Office Action at page 4, the Examiner acknowledged Applicants' assertion that the application as amended complies with the requirements of 37 C.F.R. §§ 1.821-1.825.

Withdrawn Rejections and Allowable Subject Matter

In the Office Action at page 4, the Examiner withdrew the rejections of claims 123, 158, and 166 under 35 U.S.C. § 112, first paragraph, and under 35 U.S.C. § 102(e). The Examiner also withdrew the rejection of claims 34, 119, 121, 122, 158 and 164-166 under 35 U.S.C. § 103(a).

In the Office Action at page 16, the Examiner indicated that Claim 123, as it reads on species nn. amino acids I-105 to V-113 of SEQ ID NO:2 (*see* Election of Species Requirement, Paper No. 20, at page 3), claim 158, and claim 166 are allowed.

Rejections under 35 U.S.C. § 112

Claims 84, 119, 121, 164, 165, and 210-214 have been rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Office Action, page 5. Applicants respectfully traverse this rejection.

The Examiner has acknowledged that "Applicants clearly are in possession of SEQ ID NO:2 including the amino acid sequence, I-105 to V-113." Office Action at page 6. However, the Examiner has asserted that "the balance of the fusion protein is

unknown and there is no nexus presented between the structure and function of the fusion protein." *Id.* The Examiner further asserted that "[a]t the time the application was filed, Applicants only had possession of SEQ ID NO:2 containing the amino acid epitope, I-105 to V-113 and not fusion polypeptides that include undefined amino acid sequences." *Id.* at 8. Applicants respectfully disagree with these assertions.

The test for the written description requirement is whether one skilled in the art can reasonably conclude that the inventor has possession of the claimed invention in the specification as filed. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 U.S.P.Q.2d 1111, 1116 (Fed. Cir. 1991); M.P.E.P. § 2163.02. The Federal Circuit has re-emphasized the well-settled principle of law that "[t]he written description requirement does not require the applicant 'to describe exactly the subject matter claimed, [instead] the description must clearly allow persons of ordinary skill in the art to recognize that [they] invented what is claimed,'" *Union Oil of Cal. v. Atlantic Richfield Co.*, 208 F.3d 989, 54 U.S.P.Q.2d 1227 (Fed. Cir. 2000). Furthermore, an Applicant is not required to explicitly describe the subject matter. *Unocal*, 208 F.3d at 1000; *see also* M.P.E.P. § 2163.02 ("The subject matter of the claim need not be described literally (*i.e.*, using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement."). The Court emphasized the importance of what the person of ordinary skill in the art would understand from reading the specification, rather than whether the specific embodiments had been explicitly described or exemplified. Indeed, as the court noted, "the issue is whether one of skill in the art could derive the claimed ranges from the patent's disclosure." *Unocal*, 208 F.3d at 1001.

Applicants note that the Federal Circuit stated in *Univ. of Calif. v. Eli Lilly & Co.*, 43 U.S.P.Q.2d 1398 (Fed. Cir. 1997), that:

> A description of a genus of cDNAs may be achieved by means of a recitation of [1] a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or [2] of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus . . . We will not speculate in what other ways a broad genus of genetic material may be properly described . . .

Univ. of Calif., 43 U.S.P.Q.2d at 1406. Thus, the Federal Circuit has stated that the written description requirement for a claim directed to a genus of cDNAs may be satisfied by providing the sequences of a representative number of cDNAs which fall within the scope of the genus or by providing a recitation of structural features which are common to a substantial portion of the members of the genus. *Id.*

The claims are directed to fusion proteins which comprise specifically recited C35 peptide epitopes--for which the sequences are explicitly provided--and a polypeptide from a particular recited group of polypeptides. For the reasons stated below, Applicants assert that the disclosure of the recited C35 peptide epitopes as the common structural feature, as well as the disclosed additional features (i.e., a polypeptide from the recited group of polypeptides) of the claimed invention satisfies the written description requirement.

The recited C35 peptide epitopes are clearly supported in the specification. Each of the claims requires a particular recited amino acid sequence within SEQ ID NO:2, of which the Examiner agrees that Applicants' clearly had possession, *see* Office Action at page 6, so one of skill in the art easily would be able to identify members of the genus

claimed herein. Each member will contain the unique sequences of the recited C35 peptide epitopes. The recited polypeptides, (*i.e.*, a heterologous epitope, a heterologous signal sequence, a heterologous functional domain, part of the constant domain of an immunoglobulin, and a marker sequence) are not "arbitrary polypeptides" or "undefined" as suggested by the Examiner, but rather, as shown in detail below, were known in the art such that Applicants need not describe them in detail in the specification. *See Hybritech Inc.*, 802 F.2d at 1384, 231 USPQ at 94, and MPEP §2163 at 2100-165, col. 2 (Rev. 2, Feb. 2004).[1]

Heterologous epitope

The concept of a heterologous epitope was known in the art at the time of filing of the captioned application. The specification provides ample disclosure regarding the structure and function of epitopes. *See e.g.*, Specification at paragraphs [0086]-[0093]. Clearly, a "heterologous epitope" refers to a peptide that has the known function of an epitope, but which is not a C35 peptide epitope. For instance, paragraph [0183] of the specification as filed provides, as one non-limiting example, that "[t]he C35 peptide epitope gene product or peptide fragments thereof, can be linked to a heterologous epitope that is recognized by a commercially available antibody." Since heterologous epitopes were known in the art, one of ordinary skill could readily ascertain that Applicants were in possession of a fusion protein comprising at least one of the recited

[1] At page 6 of the Office Action, the Examiner asserted that "Applicants attest that heterologous proteins are known and cite case law in support of this assertion." Applicants respectfully point out that *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, and Section 2163 of the MANUAL OF PATENT EXAMINING PROCEDURE were cited in the Reply dated October 15, 2004, not to assert that heterologous proteins are known, but rather to confirm the well-established principle that what is known in the art need not be described in the specification.

C35 peptide epitopes and a heterologous epitope without Applicants describing in detail the sequence of each known heterologous epitope.

Newly added dependent claim 215 is drawn to "[a] fusion protein according to claim 84, wherein said C35 peptide epitope is linked to a heterologous epitope." Should the Examiner maintain the rejection of the claim reciting the Markush group of polypeptides, Applicants respectfully request that the Examiner separately consider claim 215.

Heterologous signal sequence

The concept of a heterologous signal sequence to direct a protein or peptide to a particular location in a cell was also known in the art at the time of filing of the captioned application. *See e.g.*, MOLECULAR BIOLOGY OF THE CELL G-8 (Alberts *et al.*, eds., 1994) (defining "signal peptide" as a "[s]hort sequence of amino acids that determines the eventual location of a protein in the cell") (provided herewith as Attachment A). Paragraph [0035] of the present specification, for example, indicates that signal sequences may be used to direct a peptide to the ER, secretory vesicle, or extracellular space. Clearly, a "heterologous signal sequence" with respect to C35 refers to a signal sequence that is not naturally associated with C35 without some additional manipulation, for example, through recombinant molecular biology techniques that were well known in the art. Since heterologous signal sequences were known in the art, one of ordinary skill could readily ascertain that Applicants were in possession of a fusion protein comprising a C35 peptide epitope and a heterologous signal sequence without Applicants describing in detail each known signal sequence.

Dependent claim 210 is drawn to "[a] fusion protein according to claim 84, wherein said C35 peptide epitope is linked to a heterologous signal sequence." Should the Examiner maintain the rejection of the claim reciting the Markush group of polypeptides, Applicants respectfully request that the Examiner separately consider claim 210.

Heterologous functional domain

The concept of a heterologous functional domain was also known in the art at the time of filing of the captioned application. The term "functional domain refers to a region of a protein having a function, as compared to a "structural domain". *See e.g.*, MOLECULAR BIOLOGY OF THE CELL G-8 (Alberts *et al.*, eds., 1994) (defining "domain" as: "Portion of a protein that has a tertiary structure of its own") (provided herewith as Attachment B). A "heterologous functional domain" with respect to C35 clearly refers to a functional domain that is not naturally associated with C35 without some additional manipulation, for example, through recombinant molecular biology techniques that were well known in the art. Since the structure and function of heterologous functional domains were known in the art, one of ordinary skill could readily ascertain that Applicants were in possession of a fusion protein comprising a C35 peptide epitope and a heterologous functional domain without Applicants describing in detail the sequence of each known functional domain.

Dependent claim 211 is drawn to "[a] fusion protein according to claim 84, wherein said C35 peptide epitope is linked to a heterologous functional domain." Should the Examiner maintain the rejection of the claim reciting the Markush group of

polypeptides, Applicants respectfully request that the Examiner separately examine claim 211.

Part of the constant domain of an immunoglobulin

Constant domains of immunoglobulins were also well known and characterized in the art at the time of filing of the present invention. Furthermore, Paragraphs [0237]-[0238] and [0317]-[0320] of the specification as filed provide ample disclosure regarding fusion proteins comprising parts of constant domains of an immunoglobulin, including an example of a sequence of a human IgG Fc region. Hence, one of ordinary skill in the art could readily ascertain that Applicants were in possession of a fusion protein comprising a C35 peptide epitope and a part of an immunoglobulin constant domain without Applicants describing in detail the sequence of each known constant domain or part thereof.

Dependent claim 212 is drawn to "[a] fusion protein according to claim 84, wherein said C35 peptide epitope is linked to part of the constant domain of an immunoglobulin." Should the Examiner maintain the rejection of the claim reciting the Markush group of polypeptides, Applicants respectfully request that the Examiner separately examine claim 212.

Marker sequence

The concept of marker sequences was also well known and such sequences were characterized in the art at the time of filing of the present invention. Furthermore, Paragraphs [0239] and [0316] of the specification as filed provide disclosure regarding marker sequences, including as examples a hexa-histidine tag, HA-tag, protein A, IgG domains, and maltose binding protein. Hence, one of ordinary skill in the art could

readily ascertain that Applicants were in possession of a fusion protein comprising a C35 peptide epitope and a marker sequence without Applicants describing in detail each known marker sequence.

Dependent claim 213 is drawn to "[a] fusion protein according to claim 84, wherein said C35 peptide epitope is linked to a marker sequence." Should the Examiner maintain the rejection of the claim reciting the Markush group of polypeptides, Applicants respectfully request that the Examiner separately examine claim 213.

The Written Description Requirement is Met

Given the above, as required by *Unocal*, a person of skill in the art would be able to derive the claimed invention based on the novel recited C35 peptide epitopes and disclosure in the specification. Hence, Applicants respectfully assert that the written description requirement has been fulfilled.

Example 8 of the Written Description Guidelines further supports Applicants' assertion. The Example is directed to a claim comprising SEQ ID NO:2, which, according to the Example, is taught in the specification. Analysis of this claim is summarized on page 35 of the Guidelines as follows:

> Weighing all factors including (1) that the full length ORF (SEQ ID NO: 2) is disclosed and (2) that any substantial variability within the genus arises due to addition of elements that are not part of the inventor's particular contribution, taken in view of the level of knowledge and skill in the art, one skilled in the art would recognize from the disclosure that the applicant was in possession of the genus of DNAs that comprise SEQ ID NO: 2.

Synopsis of Application of Written Description Guidelines (U.S.P.T.O), page 35.

In the present case, the sequences of the specifically recited C35 peptide epitopes are disclosed, and any variability within the genus arises due to addition of elements that

are not part of Applicants' particular contribution. Heterologous epitopes, heterologous signal sequences, heterologous functional domains, constant domains of an immunoglobulin, and marker sequences were well known in the art as well as disclosed in the specification.

The Examiner asserted that "the fusion protein that comprises one C35 peptide epitope is surrounded by amino acids not described in the specification," and that "[t]he broad claim reads on a plethora of polypeptides of any length, hence there is no sufficient evidence presented in the Remarks or of record of Applicants' possession of such a huge group of polypeptides." Office Action at page 8. For the following reasons, Applicants respectfully assert that the genus encompassed by the claims is not nearly so diverse as the Examiner argues. This is because it was known by the earliest claimed priority date that epitopes are typically processed from larger proteins by intracellular proteosomes that recognize cleavage sites adjacent to the epitope, thus allowing binding of the processed epitope to HLA. Del Val *et al.*, *Cell* 66:1145-1153 (1991) (submitted herewith as document AS29); Eisenlohr *et al., J.Exp.Med.* 175:481-487 (1992) (submitted herewith as document AT29). Del Val *et al.* produced chimeric proteins containing a known epitope at different positions within an unrelated protein. Del Val *et al.*, abstract. They found that although the yield of processed epitope differed depending on the positioning of the epitope within the chimera, the chimeras *were*, nonetheless, correctly processed to produce the epitope. *Id.*, abstract and 1149, col. 2, 3d full paragraph. Eisenlohr *et al.* also showed that flanking residues influence epitope processing. Eisenlohr *et al.*, abstract. They also showed that the "the effect of negatively acting flanking sequences can be overcome by additional flanking sequences." *Id.*, 485,

col. 2, 3d paragraph. The results of Del Val *et al.* and Eisenlohr *et al.* were reviewed in Yewdell and Benninck, *Adv. Immunology 52*:1-123 (1992) (submitted herewith as document AR30). Yewdell and Benninck summarized other studies in which epitopes were placed in recombinant proteins and were able to be processed no matter where they were located. Yewdell and Benninck at 31-32.

Applicants further draw the Examiner's attention to *Ex parte Fisher*, a non-binding decision of the Board of Patent Appeals and Interferences. Ex Parte Fisher, 72 USPQ2d 1020 (B.P.A.I. 2004) (provided herewith as Attachment C). This recent decision, while non-binding on the Board, provides guidance with respect to the Board's thoughts on molecules comprising short sequences, in that case, expressed sequence tags (ESTs). As the Examiner is aware, ESTs are short nucleotide sequences randomly selected from cDNA libraries. The claim at issue in *Fisher* was drawn to a substantially purified nucleic acid molecule encoding a fragment of a maize protein comprising a nucleic acid sequence selected from a group of five EST sequences. Although nothing was known of the peptide fragments encoded by these sequences and the claim used the open transitional phrase "comprising," the Board held that there was adequate written description support in the specification and overturned the Examiner's rejection under 35 U.S.C. section 112, first paragraph. *Id.* The Board stated "[t]hat the claimed nucleic acid molecules may have other molecules attached to either, or both of their 5' or 3' ends does not diminish appellants' adequate written description of the nucleic acids [*sic*] molecules with the sequence set forth in SEQ ID NO:1 through SEQ ID NO:5." *Id.* at page 26.

Applicants submit that the present claims do not read on a genus more varied than that encompassed by a nucleotide sequence comprising an EST sequence. As the

Board has held that such claims have adequate written description on the basis of the disclosed EST sequence information, Applicants assert that the instant specification contains at least as much support and the rejection should be withdrawn.

Applicants assert that one of skill in the art would readily recognize Applicants' possession of the claimed invention. Accordingly, Applicants respectfully assert that the claimed invention has been adequately described and respectfully request that the rejection under 35 U.S.C. § 112, first paragraph be reconsidered and withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph - enablement

Claims 84, 119, 121, 164, 165 and 210-214 are rejected under 35 U.S.C. 112 first paragraph, as allegedly being nonenabled for their full scope. Office Action, page 9. Applicants respectfully traverse this rejection.

The test of enablement is whether one of ordinary skill in the art, given the disclosure at the time of filing, could make and use the claimed invention without undue experimentation. *See In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The Examiner addressed several of the "*Wands*" factors to be considered when determining whether experimentation is "undue." *See id.*; (Office Action at pages 11-12). As stated in *Wands*, "'[t]he key word is "undue," not "experimentation."'" *Wands* at 737 (quoting *In re Angstadt*, 537 F.2d at 504, 190 USPQ at 219).

Nature of the invention and breadth of the claims

With respect to the nature of the invention, the Examiner asserted that "The invention is in a class of invention which the CAFC has characterized as 'the

unpredictable arts such as chemistry and biology.'" Office Action at page 10 (citations omitted).

With respect to the breadth of the claims, the Examiner asserted that:

> The claims are broadly drawn to a fusion protein comprising a defined C35 peptide sequence, I-105 to V-133. . .and undefined amino acid sequences broadly identified as a heterologous epitope, a heterologous signal sequence, a heterologous functional domain, part of the constant domain of an immunoglobulin and a marker sequence. The breadth of the claims is vast and not reasonably supported by the specification.

Id. Applicants respectfully disagree with the Examiner's assertions.

The amino acid sequences of the recited group of polypeptides are not "undefined" as suggested by the Examiner. Rather, as set forth in the preceding section of this Reply, this list specifically recites polypeptides that are encompassed by the claimed invention, and the specification provides ample guidance as to what these types of polypeptides are. *See e.g.*, Specification at paragraphs [0183] (heterologous epitopes), [0237]-[0238] (part of the constant domain of an immunoglobulin), [0239] (marker sequences), and [0316] (heterologous signal sequences). It is not necessary that the specification set forth each and every amino acid sequence of each and every one of the possible polypeptides because these are readily determinable by one of ordinary skill in the art. Therefore, Applicants respectfully submit that the claims are not overly broad.

Quantity of experimentation needed to make or use invention

The Examiner asserted that:

> The quantity of experimentation in this area is extremely large since heterologous epitope, a heterologous signal sequence, a heterologous functional domain, part of the constant domain of an immunoglobulin and a marker sequence have not been clearly defined by the specification.

Office Action at page 11. Applicants respectfully disagree with these assertions.

The fact that some experimentation may be required does not preclude enablement, so long as the experimentation is not undue. *Wands*, 858 F.2d at 736-737. "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Id.* at 737. Contrary to the Examiner's assertions, as stated above, the specification does provide specific guidance to practice the invention, including guidance on fusion proteins comprising heterologous epitopes, part of the constant domain of an immunoglobulin, functional domains, marker sequences, and heterologous signal sequences. *See e.g.*, Specification at Paragraphs [0182]-[0185], [0233]-[0240], and [0316]-[0320].

The Examiner further asserted that "it is not clear what the limits are of a 'part of a constant domain'. This recitation in itself reads on a couple of amino acids or many amino acids." Office Action at page 11. Applicants respectfully submit that, as set forth in detail above, immunoglobulin constant domains were well known in the art. In addition, Example 8 of the captioned application provides as a non-limiting example a human IgG Fc region sequence, and provides ample direction and guidance regarding how to make a fusion protein. *See* Specification at Paragraphs [0316] to [0320].

Finally, according to the Examiner, "[w]hile it is clear Applicants desire to implement these fusion proteins in the treatment of C35-specific cancers, in diagnostic and prognostic applications it would require significant study to identify, make and use

the exponential amount of fusion proteins that are applicable to treatment, diagnosis, and prognosis." Office Action at page 11. Applicants respectfully disagree.

Claim 84 and its dependent claims are directed to a fusion protein which comprises a specifically recited C35 peptide epitope and a polypeptide selected from a group of specifically recited polypeptides. Applicants respectfully maintain that adequate guidance and direction to practice the claimed invention are provided in the specification. One of ordinary skill in the art would be able to make and use the claimed invention, for example in the diagnosis or prognostic testing of C35-specific cancer as disclosed throughout the specification. Furthermore, the specification provides that C35 polypeptides and fusion proteins which comprise CTL epitopes are useful in the treatment of C35-specific cancers. In Example 2, for example, on pages 227-229 of the specification as filed, the inventors have shown that CTLs specific for a C35 epitope kill breast cancer cells. Thus the specification provides adequate guidance as to how C35 peptide epitopes and fusion proteins can be used.

Level of predictability in the art and state of the prior art

With respect to the level of predictability in the art and state of the prior art, the Examiner asserted that:

> . . . predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar activity requires a knowledge of and guidance with regard to which amino acids or acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved and detailed knowledge of the ways in which the protein's structure relates to its function. The specification provides essentially no guidance as to which of the infinite possible choices is likely to be successful.

Office Action at page 11. Applicants respectfully disagree with the Examiner's contentions.

Contrary to the Examiner's assertion that there are "infinite possible choices," the claims recite specific C35 peptide epitopes and specific polypeptides. Applicants respectfully assert that, as detailed above, the specification provides ample guidance as to how to make and use the claimed fusion proteins at, *inter alia*, Specification Paragraphs [0182]-[0185], [0233]-[0240], and [0316]-[0320], which describes fusion proteins and cites numerous references discussing fusion proteins. Furthermore, standard, well-known techniques of molecular biology can be used for generating fusion proteins.

The Examiner cites Lazar *et al.*, *Molecular and Cellular Biology* 8:1247-1252 (1988), as evidence to support the assertion that "the introduction of mutations in an amino acid sequence will yield products with different biological activity from the wild type protein." Office Action at page 11.

Applicants respectfully disagree with the Examiner's characterization of Lazar *et al.* that every amino acid modification will necessarily yield products with different biological activity from the wild type protein. Rather, Lazar *et al.* compared the amino acid sequences of numerous EGF-like peptides and determined which amino acid residues are conserved in the family of proteins. They then predicted, based on their assessment, which amino acids of the TGF-α sequence were likely to result in a change of biological function of the protein if mutated. Thus, if anything, Lazar *et al.* demonstrate the predictability of making amino acid modifications. This is further supported at Paragraphs [0064]-[0070] of the present specification, which describes the tolerance of proteins for amino acid substitutions. Thus, the Examiner's mere assertion

that "it would *seem* the amino acid sequences surrounding the C35 peptides (i.e., amino terminal, carboxy terminal) would affect structure and function of the fusion proteins and inevitably influence their use in the suggested applications" is unsubstantiated.

Furthermore, as set forth above with respect to written description, Applicants respectfully assert that addition of molecules to the peptide epitope does not necessarily affect its function. Indeed, peptide epitopes that are capable of retaining their function within the context of a larger peptide or molecule (e.g., epitopes with flanking sequences) are well known in the art. As discussed above, Del Val *et al.* produced chimeric proteins containing a known epitope at different positions within an unrelated protein. Del Val *et al.*, abstract. They found that although the yield of processed epitope differed depending on the positioning of the epitope within the chimera, the chimeras *were*, nonetheless, correctly processed to produce the epitope. *Id.*, abstract and 1149, col. 2, 3d full paragraph. Eisenlohr *et al.* also showed that flanking residues influence epitope processing. Eisenlohr *et al.*, abstract. They showed that the "the effect of negatively acting flanking sequences can be overcome by additional flanking sequences." *Id.*, 485, col. 2, 3d paragraph. The results of Del Val *et al.* and Eisenlohr *et al.* were reviewed in Yewdell and Benninck, *Adv. Immunology 52*:1-123 (1992). Yewdell and Benninck also summarized other studies in which epitopes were placed in recombinant proteins and were able to be processed no matter where they were located. Yewdell and Benninck at 31-32. These references demonstrate that evaluating activity of epitopes comprising additional amino acids is routine. They also demonstrate that the function of epitopes comprising additional amino acids is achieved with a high frequency of success.

Accordingly, the level of predictability and state of the art would require one of ordinary skill to engage in no more than routine experimentation to practice the invention.

Existence of working examples and guidance in the specification

With respect to the amount of direction provided by the inventor and the existence of working examples, the Examiner asserted that the specification provides insufficient guidance in terms of the selection of sequences of a heterologous epitope, a heterologous signal sequence, a heterologous functional domain, part of the constant domain of an immunoglobulin and a marker sequence, and that one of ordinary skill in the art would be forced "to determine through trial and error which fusion proteins would be effective for treatment, diagnosis, and prognosis. Office Action at page 12. The Examiner further asserted that "[t]he disclosure provides insignificant objective evidence and insufficient working examples to lead one or ordinary skill in the art [to] a reasonable expectation of success." *Id.*

Applicants respectfully remind the Examiner that "[t]he specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation." M.P.E.P. § 2164.02 at 2100-187 (citing *In re Borkowski*, 422 F.2d 904, 908, 164 U.S.P.Q. 642, 645 (CCPA 1970)). Furthermore, in the present case, Applicants do provide examples, even though they are not required. However, the disclosure is not limited to the examples. "How a teaching is set forth, by specific example or broad terminology, is not important." M.P.E.P. § 2164.08 at 2100-198 (citing *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 370 (CCPA 1971)). As set forth, *supra*, the

present specification provides extensive disclosure on how to make and use fusion proteins at, *inter alia*, Paragraphs [0182]-[0185], [0233]-[0240], and [0316]-[0320], and including that C35 polypeptides and fusion proteins which comprise CTL epitopes are useful in the treatment of C35-specific cancers. In Example 2, for example, at Paragraphs [254]-[256], the inventors have shown that CTLs specific for a C35 epitope kill breast cancer cells. Thus, there is ample direction provided in the present specification, some in the form of examples. Furthermore, any experimentation required to practice the invention in light of the specification would be routine, as demonstrated by Del Val *et al.*, Eisenlohr *et al.*, and Yewdell and Benninck.

The Enablement Requirement is Met

The analysis of the various factors for determining whether the experimentation required to practice the claimed invention would be undue, clearly shows that it would not be. Namely, the claims are not overly broad in light of the extensive disclosure of the various aspects of the invention. Moreover, the state of the art and level of predictability in the art at the time of filing were such that, given the disclosure, one of ordinary skill in the art could practice the invention. Furthermore, one of ordinary skill in the art, given the specification, could make and use the invention without undue experimentation because there is ample direction provided in the specification, and there are examples to illustrate various aspects of the present invention. The weighing of these factors indicates that the claims are enabled. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 84, 119, 121, 164 and 210-214 are rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Office Action at page 14. Applicants respectfully traverse this rejection.

The Examiner asserted that "[c]laim 84 is vague and indefinite in the recitation 'a heterologous functional domain'. It is not clear what functions the domain should possess. Accordingly, the metes and bounds cannot be determined." Office Action at page 14. Applicants respectfully disagree with this assertion. The term "functional domain" is well known in the art, and refers to a region of a protein having a function (as compared to a "structural domain"). *See e.g.*, MOLECULAR BIOLOGY OF THE CELL G-8 (Alberts *et al.*, eds., 1994) (defining "domain" as: "Portion of a protein that has a tertiary structure of its own.") (provided herewith as Attachment B). Given the knowledge in the art, and in light of the specification, Claim 84 would reasonably apprise one skilled in the art of the metes and bounds of the claimed invention. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Rejections under 35 U.S.C. § 102

Claims 84, 119, 121, 164, 165 and 210-214 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent Application Publication No. US2002/0052308A1. Office Action, page 14. Applicants respectfully traverse the rejection.

US2002/0052308A1 discloses a protein 131 amino acids in length (SEQ ID NO:966). Although the peptide epitope I-121 to V-129 is contained within this 131 amino acid protein, this reference does not provide any description or suggestion of the ITNSRPPCV peptide itself.

The Office Action states that the disclosed C35 peptide epitope is comprised amongst 122 additional amino acids, which read on Applicants' claimed fusion protein. Office Action, page 14. Applicants note that claim 84 (and all pending claims depending from claim 84) are directed to a fusion protein comprising *a C35 peptide epitope* and a polypeptide selected from a group of recited polypeptides which includes a heterologous epitope, a heterologous signal sequence, a heterologous functional domain, part of the constant domain of an immunoglobulin, and a marker sequence. The cited publication, thus, does not teach or suggest the fusion protein of claims 84, 119, 121, 164, 165 or 210-214. Accordingly, the cited publication does not anticipate these claims.

Applicants respectfully maintain that, in the absence of a specific teaching or suggestion to make these *particular recited peptide epitopes,* the cited publication cannot anticipate or render obvious the claimed invention. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Reply is respectfully requested.

Respectfully submitted,

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